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Effect of Sensory Stimuli on Restless Legs Syndrome: A Randomized Crossover Study

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SCIENTIFIC INVESTIGATIONS

Study Objective: A variety of sensory stimuli relieve restless legs syndrome symptoms. Because systematic evaluations of sensory stimulation in restless legs syndrome are largely lacking, we performed a randomized crossover study to evaluate the effect of external sensory stimulation on restless legs syndrome symptoms.

Methods: Eighteen patients underwent 3 consecutive suggestive immobilization tests with the order of the following 3 conditions randomly assigned: no electrical stimulation (condition 1), tactile and proprioceptive sensory stimulation (condition 2), and tactile sensory stimulation only (condition 3). Restless legs syndrome symptoms were quantified by visual analog scales, and periodic leg movements during wake were measured.

Results: Baseline visual analogue scale score was 4.5 (range 0-60) in condition 1, 10.5 (range 0-96) in condition 2, and 8.5 in condition 3 ($p = 0.21$). There was a tendency towards a higher maximum visual analogue scale score and visual analogue scale score at the end of the suggested immobilization test in the conditions with tactile sensory stimulation, though not significant ($p = 0.74$ and $p = 0.29$, respectively). Fifteen patients suffered from periodic leg movements during wake. Median indices were 18 (range 0-145) in condition 1, 26 (range 0-190) in condition 2, and 49 (range 0-228) in condition 3 ($p = 0.76$).

Conclusions: We found a tendency towards less leg discomfort in the conditions in which an external sensory input was applied. This potential benefit of sensory stimuli on restless legs syndrome severity merits further investigation as this could open new ways towards a better pathophysiological understanding and non-pharmacological treatments.

Keywords: restless legs syndrome, suggestive immobilization test, periodic limb movement disorder

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Restless legs syndrome (RLS) is characterized by an urge to move combined with the occurrence of unpleasant or disabling sensory symptoms at rest. These symptoms begin or worsen during rest or inactivity and occur mostly during the evening or night. They are relieved by voluntary movement, at least as long as the activity continues.[1] Eighty to 90 percent of RLS patients also suffer from involuntary periodic limb movements during wake (PLMW) or sleep (PLMS).[1,2,3]

Clinical experience shows that, besides movement of the legs, a variety of sensory stimuli may relieve RLS symptoms. Cold showers, massaging of the legs, or a hot bath may lessen RLS symptoms.[4] One case study showed that a massage program reduced RLS complaints.[5] In addition, several studies report a positive effect on RLS symptoms with the use of external compression on the legs. Eliasion and Lettieri showed a positive effect on RLS severity and improvement of fatigue and daytime sleepiness with the use of sequential compression devices.[6,7] Moreover, Rajaram and colleagues reported a reduction in RLS symptoms in RLS patients that were treated with enhanced external counter pulsation (EECP) on the legs for congestive heart failure.[8] Nevertheless, a follow-up double-blind, placebo-controlled study showed no difference in reduction of RLS symptoms between the therapeutic EECP and placebo.[9]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Clinical experience shows that a variety of sensory stimuli may relieve RLS symptoms, though systematic evaluations of these phenomena are lacking. We performed a randomized crossover study to evaluate the effect of external sensory stimulation on restless legs syndrome symptoms.

Study Impact: External sensory input tends to reduce leg discomfort in patients suffering from restless legs syndrome. This potential benefit could open new ways towards a better pathophysiological understanding and non-pharmacological treatments.

The positive effect of these local leg compression devices on RLS complaints may be attributed to an improved local circulation and decrease of subclinical local ischemia.[7,8] Nevertheless, one could also hypothesize that it is not the repetitive compression but repetitive sensory input on the legs that reduces the RLS symptoms.

To objectify the phenomenon of sensory input reducing RLS complaints, we performed a randomized crossover study in

which an external sensory stimulus at the ankle of RLS patients was applied.

METHODS

Participants

Patients were recruited from the outpatient clinic of both the Center for Sleep and Wake disorders, Medical Center Haaglanden the Hague and the Department of Neurophysiology, St Antonius Hospital/Nieuwegein. Patients had to meet the essential criteria for RLS.[1] Furthermore, all patients had to suffer from moderate to severe RLS as defined by the John Hopkins Restless Legs Severity scale (JHRLSS, score ≥ 2)[10], a score ≥ 15 on the International Restless Legs Study Group rating scale (IRLS)[11] and had to report symptoms of RLS 6-7 days a week. Secondary RLS was ruled out by blood analysis (on total blood count, iron deficiency, thyroid function, glucose, renal function) and physical neurological examination.

Patients were not allowed to use any pharmacological treatment for RLS during the study. If patients used RLS specific drugs, they were asked to stop these 2 weeks prior to the study. Patients were excluded if they suffered from any other neurological disorder (including sleep disorders other than RLS) or psychiatric disease; patients were not allowed to use antidepressants.

Thirty-six patients were willing to participate in the study. Fifteen patients were excluded—4 because of the use of neuroleptics that could not be stopped, 7 because of comorbidities like low ferritin levels, diabetes mellitus, and hypothyroidism; 4 patients did not meet RLS severity criteria. Twenty-one patients were included in the study. Two patients withdrew from participation after inclusion because of the large travel distance. One patient was excluded for technical reasons (irreproducible SSEPs).

The local ethics committee (METC Zuid-West Holland;07-042) approved the study. All details and risks of the study were explained to the participants verbally and in writing and all gave written informed consent.

Study Design

All procedures were performed at the Medical Center Haaglanden. The measurements were performed in the evening at the time most RLS patients experience symptoms. All patients underwent 3 consecutive suggested immobilization tests (SIT).

Suggested Immobilization Test (SIT)

The SIT is a diagnostic tool developed to evaluate the effect of immobility on the severity of the sensory and motor symptoms of RLS during wakefulness.[12,13] The first SIT started at 8.30 PM; between consecutive SITs the patients were allowed to walk around for 10 minutes. Each independent SIT had a duration of 30 minutes. During the tests patients remained in bed, reclined at a 45° angle with their legs extended (see picture 1). They were instructed not to make any voluntary movements and stay awake for the entire duration of the test. If patients closed their eyes during the SIT, they were tapped on their arm and reinstructed to stay awake and keep their eyes open.

During the SIT, 3 different study conditions (see below) were performed. Because RLS severity increases over time in the evening and night, conditions were counterbalanced and the order randomized for each patient over the 3 consecutive SITs. The 3 study conditions during the three independent consecutive SITs were:

1. SIT without electrical stimulation;
2. SIT with electrical stimulation of the posterior tibial nerve on one leg. The posterior tibial nerve was stimulated adjacent to the medial malleolus. The intensity of the electrical stimulus was adjusted until a twitch of the big toe was seen. The pulse duration of the stimulus was 0.2 ms; the frequency was 3 Hz.
3. SIT with electrical stimulation with the same stimulus intensity as in study condition 2, only in this condition the stimulator was placed a little aside from the nerve to prevent movement of the big toe. The same pulse duration and frequency were used as in condition 2.

Condition 3 was added to measure solely the tactile sensory effect as compared to condition 2, in which besides a tactile sensory effect, a proprioceptive sensory effect was generated due to movement of the big toe. Patients were randomized to receive the stimuli on either the right or the left ankle.

Simultaneous with electrical external stimulation, somatosensory evoked potentials (SSEPs) were performed to ascertain cortical processing of the stimulus.

Leg Discomfort

To measure the degree of leg discomfort during the 3 different SITs, patients were asked to rate their leg discomfort on a visual analogue scale (VAS) every 5 minutes. The VAS has been used before to assess severity of RLS complaints.[14,15] It consisted of a 100 mm line marked 0 on one end and 100 on the other, with 0 mm representing no discomfort at all and 100 mm indicating the worst discomfort experienced. A visual message signaled the patient to complete the scale; VAS scores were obtained at baseline and every 5 min until the end of every SIT—in total 7 times.

In addition to the consecutive VAS scores, periodic leg movements during wake (PLMW) were monitored during the 3 SITs. To measure PLMWs, the anterior tibial muscle activity was monitored using surface electrodes placed on the lower third of the right and left legs. For this, we used the device that is also used in our sleep laboratory to measure leg activity during sleep in our outpatients (ambulant polysomnography). PLMWs that occurred during generalized body movement were excluded from analyses. The anterior tibial muscle activity was recorded at a time constant of 0.3 s and a high-band filter setting at 90 Hz. The PLMWs were scored according to the Official World Association of Sleep Medicine (WASM) standards for recording and scoring PLMW.[16] The periodic limb movement index ([PLMI] PLMWs per hour of SIT) was calculated.

Statistical Analysis

Planned analyses compared all VAS scores at baseline (time: 0 minutes), VAS scores at the end of each SIT (time 30 min) and the maximum VAS score during the SIT between the 3 conditions. Friedman tests for related samples were performed to evaluate if there was any significant difference in these VAS

Table 1—Leg discomfort, as scored on VAS, according to condition

	Condition 1	Condition 2	Condition 3	p value*
Baseline VAS (mm), median (range)	4.5 (0-60)	10.5 (0-96)	8.5 (0-65)	0.21; ns
End VAS (mm), median (range)	69.5 (6-98)	49.5 (5-95)	46.0 (0-98)	0.29; ns
Maximum VAS (mm), median (range)	69.5 (10-98)	58.5 (10-98)	57.5 (10-98)	0.74; ns
PLMI (n = 15), range	18 (0-145)	26 (0-190)	49 (0-228)	0.76; ns

Condition 1, Suggested Immobilization Test with no electrical stimulation; Condition 2, Suggested Immobilization Test with tactile and proprioceptive sensory stimulation; Condition 3, Suggested Immobilization Test with tactile sensory stimulation only (for details see Methods). VAS, visual analogue scale; PLMI, periodic limb movement index; NS, not significant. * Friedman test of related samples.

scores between the 3 conditions. The change in VAS over time was compared between the 3 conditions using a linear mixed model including an interaction term of condition with time. For patients also suffering from PLMWs, the PLMIs were compared between the 3 conditions were compared using the Friedman test of related samples. P levels with a value of less than 0.05 were considered significant. All analyses were performed with SPSS version 19.

Due to the lack of (to our best knowledge) previous studies on the effect of external sensory input on RLS symptoms, we were not able to make a sample size calculation. However, we calculated that including 18 patients would be sufficient to detect a standardized difference in VAS between the test conditions of 1.0, with a power of 80% and two-sided α of 5%.

RESULTS

Eighteen RLS patients completed the study protocol—10 males and 8 females. Median age was 50 years (range; 31-69 y). All patients were diagnosed with primary RLS. The median IRLSS score was 26 points (range: 15-38). Fifteen patients also suffered from periodic limb movements during wake. Five patients had been treated for RLS symptoms (3 used pramipexol, 2 benzodiapines). In all 5 patients, medications were stopped 2 week prior to the study.

Leg Discomfort

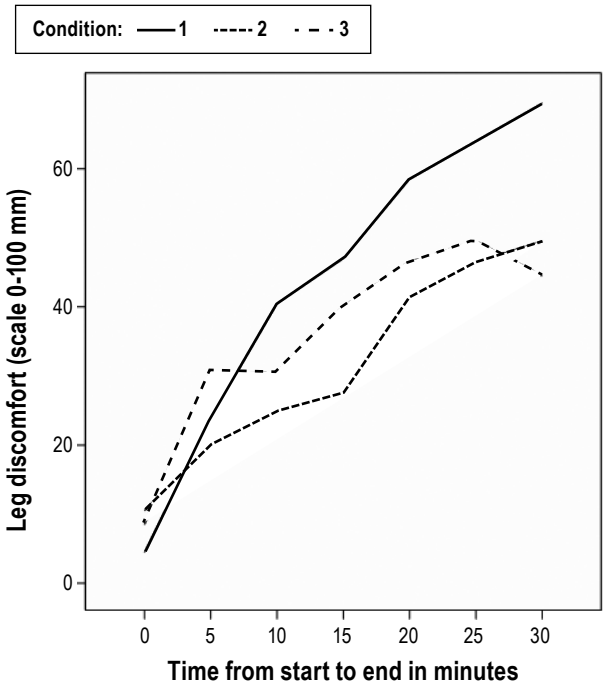
The median VAS scores for leg discomfort at baseline prior to SIT without additional intervention (condition 1), SIT with electrical stimulation of the posterior tibial nerve (condition 2) and SIT with electrical stimulation aside of the posterior tibial nerve (condition 3) were not significantly different (p = 0.21, **Table 1**).

The median VAS scores at 30 min (the end of the SIT) were the highest in condition 1 (69.5; min-max, 6-98) and the lowest in condition 3 (46.0; min-max, 0-98). The maximum VAS scores during the sit were lower in conditions 2 (58.5) and 3 (57.5) than condition 1 (69.5). However, these differences were not significant (p = 0.29, **Table 1**). VAS score increased significantly during SIT in all 3 conditions (p < 0.01), although this was not different between the 3 conditions (p > 0.05, **Figure 1**)

Periodic Limb Movement Index

Fifteen patients also suffered from PLMWs during the consecutive SITs—7 males and 8 females. The median PLMW indices (min-max) per condition were 18 (0-145) for condition 1; 26 (0-190) for condition 2; and 49 (0-228) for condition 3.

Figure 1—Median leg discomfort over the 30-minute suggested immobilization test.



Median leg discomfort scores over the 30-min suggested immobilization test (SIT) with no electrical stimulation (condition 1), tactile and proprioceptive sensory stimulation (condition 2), and tactile sensory stimulation only (condition 3, for details see Methods).

There were no significant differences in PLMI between the different conditions (Friedman test, p = 0.76).

DISCUSSION

We performed a randomized crossover study to measure the effect of external sensory stimuli on RLS severity during three consecutive SITs using both subjective (leg discomfort measured by VAS-score) and objective measurements (PLMW). No significant differences were found in leg discomfort and PLMW between the different conditions, meaning that we were not able to show a significant effect of the external sensory input given on RLS symptoms. However, there was a tendency towards lower VAS scores at the end of the SIT and the maximum VAS score in the two conditions in which an external sensory stimulus was applied.

To the best of our knowledge, this is the first study that investigated the effect of external electrical sensory input at the ankle on RLS symptoms. Massage, external compression device, or pneumatic devices showed relief of RLS symptoms.[6,7,8,9] Though these studies primarily refer to a vascular explanation for this relief, one could also argue that the external sensory input generated this positive effect. A parallel double-blind placebo-controlled study, in which enhanced external counter pulsation (EECP) was studied as therapeutic device for RLS, showed an positive effect on RLS complaints both in patients receiving EECP therapy and in the placebo group.[9] The placebo therapy consisted of identical sham devices that were inflated and deflated to a lower pressure as in EECP[9], suggesting that the sensory input of the compression devices is responsible for the improvement of RLS symptoms. This is in line with our findings of a tendency towards less leg discomfort during the SIT if an external input was applied.

This study has potential limitations. First, all measurements were done on the same evening. As RLS symptoms may increase in intensity as the evening progresses, one might expect that the last performed condition would show the worst VAS scores. However, to overcome this, we counterbalanced the order in which patients underwent the three conditions. Second, one could argue that the 30 minutes duration of the SIT procedure was too short to demonstrate significant effects, as the original protocol for the SIT the duration was 60 minutes.[13] However, differences in RLS severity scores and PLMWs can already be detected in a SIT with a duration of ten minutes.[17] Finally, our a priori sample size estimation indicated that with 18 patients, we would be able to detect a standardized difference (mean difference/standard deviation) in VAS between test conditions of 1.0. Unfortunately, our VAS data were non-normally distributed, and additional patients should have been included to obtain the intended power.

This study did not find a significant difference in VAS severity over time and PLMI during a SIT between the three different study conditions. A possible explanation could be the unpleasant nature of this electrical stimulus in itself. It might have been difficult for participants to differentiate between the "real" RLS symptoms and the discomfort from the electrical stimulus. Another possible explanation for the lack of significance is inclusion bias, as only patients with severe RLS were included. This group might suffer from too severe RLS to have any response on therapy based on sensory input alone. In addition, the sensory input as given in our study might have been to localized. Alternatively, it could be postulated that due to the non-normal distribution of VAS scores in our patients, the study was undersampled which resulted in the detection of only a trend for lower VAS scores in conditions in which an external sensory input was applied.

In conclusion, we were not able to show a significant improvement of RLS symptoms after the appliance of an external electrical stimulus. However, we did find a small trend towards lower VAS scores in conditions with external sensory input. This potential benefit merits further investigation since this could open new ways to better pathophysiological understanding and to non-pharmacological treatments of RLS.

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DISCLOSURE STATEMENT

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